

# The Role of Oxidative Stress in Alzheimer's Disease

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## Abstract

Alzheimer's disease (AD) is a growing health care epidemic. It is the most common cause of dementia in the elderly and its incidence is rising. The disease is progressive, irreversible and debilitating. It is a great burden on both the patient and their caregivers. The two pathological hallmarks of the disease are aggregated beta-amyloid deposits and hyperphosphorylated neurofibrillary tangles. Although these lesions are found in the AD brain, their role in the pathogenesis leading to clinical dementia is largely unknown and still under debate. Age, which influences the oxidative and inflammatory states of the brain, is the most important risk factor. Recent research has highlighted the important role of oxidative stress, the role of the mitochondria in early disease and inflammation in the underlying molecular mechanism of AD. Oxidative damage predominately involves lipid peroxidation from reactive oxygen species derived from metabolism. Most patients are diagnosed after irreversible damage has been done. A better understanding of the role of these stressors could lead to early therapeutic interventions that better target the cause and have potential to modify disease course. Currently there is no disease modifying treatments available. This literature review highlights current knowledge regarding the role of oxidative stress, how it relates to the pathogenesis of AD and how further research in this field can benefit those who suffer from this debilitating disease.

**Keywords:** Lipid peroxidation; Neurofibrillary tangles; Beta-amyloid deposits

## Statistics and Significance

Dementia is a progressive debilitating syndrome of dysfunction in several intellectual domains including memory, language, visuospatial ability, praxis, gnosis and executive functioning. Alzheimer's disease (AD), the most common cause of dementia, affects 35 million people worldwide including 5.5 million Americans [1]. It is an irreversible disease that causes severe functional impairment and personality changes that lead a severely compromised quality of life with complete dependence on caretakers. AD is a growing health care epidemic. Between 2000 and 2010, the proportion of deaths attributed to AD increased by 68% [2]. In 2050, the incidence of AD is expected to approach nearly a million people per year, with a total estimated prevalence of 11 to 16 million people in the USA [3,4]. The major reason for this rapid growth is that the people at greatest risk are the elderly, the fastest growing segment of the population. Age is the most significant risk factor with an incidence that doubles every 5 years after the age of 65 [1]. AD is the sixth leading cause of all deaths in the United States, and the fifth leading cause of death in Americans aged 65 and older. It is estimated that nearly 20% of the population between 65-75 has AD [3,5]. Significant cost implications related to AD and other dementias include an estimated \$200 billion annually [2,3,5].

## AD Pathogenesis

AD is a progressive neurodegenerative disease that affects the hippocampus and cortex. Although the details remain unknown, a complex interplay of genetics, environment and aging likely culminate in disease. Although specific mutations involving the beta-amyloid precursor protein have been identified in early-onset familial AD, they account for less than 5% of the cases [6]. In the majority of the cases the disease is sporadic. Multiple genes and acquired mutations likely play a role. It has been known for decades that apolipoprotein E allele variations are associated with the non-familial late-onset AD. The e4 allele confers an increased risk whereas the e2 allele reduces the risk. There is growing evidence implicating the complement pathways in the pathogenesis of AD [7,8]. Dysregulation of the complement cascade may contribute to the pathophysiology of AD. Alterations in complement signalling pathways may influence microglia function

resulting in reduced ability to phagocytose apoptotic cells and clear beta-amyloid [9]. CR1, the receptor for the complement fragments C3b and C4b, plays a role in the clearance of amyloid plaques [10]. Recent genome-wide association studies have indicated that genetic variations in CR1 are associated with global cognitive decline and higher burden of AD brain pathology [11]. Studies have shown that patients with the CR1 gene mutations have less brain amyloid and an increased risk for AD. This may mean that the CR1 gene is responsible for other factors, such as increasing the inflammation in the brain which may predispose the onset of the disease. This exciting finding puts into question the importance of beta-amyloid burden in the development of AD and is driving further research into other pathological mechanisms [12]. Other loci identified include bridging integrator (BIN1), clusterin (CLU) and ATP-binding cassette sub-family A member 7 (ABCA7). Sequencing studies have identified disease-specific variants. Genetic polymorphisms in these genes can affect cellular single transduction pathways and higher risk of cognitive decline. Animal models indicate that blocking the complement cascade can result in slower cognitive decline [7].

The macroscopic manifestation is diffuse cortical atrophy. Microscopically, there are two neuropathological lesions. Extracellular beta-amyloid (A-beta) peptide deposits (senile plaques) are the earlier AD lesions. A-beta is a 39-42 residue membrane-spanning peptide whose physiological function is not well defined. This peptide is a product of cleavage from the larger amyloid-beta protein precursor by enzymes called secretases. A-beta accumulation results from an imbalance between production and clearance. The peptide tends to be secreted after its production and thus can trigger the formation of senile plaques.

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The longer 42 residue variant of A-beta is particularly neurotoxic and has a higher tendency to aggregate and form insoluble plaques [13]. A-beta plaques accumulate in the cortex leading to cellular damage and cerebral amyloid angiopathy. Beta-amyloid peptide can also be internalized by the interaction with membrane receptors. Once inside the neuron, it interacts with organelles, including mitochondria and nucleus and can affect gene expression [14]. In addition intraneuronal beta-amyloid has been shown to cause synaptic depression accelerating memory loss in mouse models [15].

At the later stages of AD, beta-amyloid plaques trigger hyperphosphorylation of tau leading to intracellular neurofibrillary tangles which cause more cellular damage. Tau is a microtubule associated protein that changes conformation during phosphorylation. Both of these lesions involve the accumulation of insoluble aggregated proteins due to inappropriate protein conformations and appear to be later manifestations of the molecular process. The current view is that pathological processes start decades before the clinical manifestations [16]. This underscores the need to focus molecular mechanisms and early screening tests so that intervention can occur before irreversible damage.

A hypersensitive reaction, involving the innate immune system, has been linked to AD pathology [17,18]. Increased expression of inflammatory cytokines may induce beta-amyloid deposits and senile plaques. These plaques are rich in activated microglia and complement proteins underscoring the importance of inflammation in the pathogenesis. Microglia release a wide variety of pro-inflammatory mediators including cytokines, complement components and free radicals, all of which potentially contribute to further neuronal dysfunction and eventually death [19]. This neuroinflammatory process leads to ROS production, synapse dysfunction and loss of calcium regulation, which is known to be important for neurotransmission. Due to the changes in the inflammatory process that naturally accompany aging, these insults are more likely to lead to a chronic progressive response [20]. Loss of blood brain barrier integrity may lead to protein translocation into the cerebrospinal fluid, exacerbating the pro-inflammatory state of the cerebrum [20]. These processes can go on for 10-15 years prior to the onset of symptoms [21].

## AD Diagnosis

Currently, AD is a purely clinical diagnosis, based on a set of observable criteria that evaluate progressive cognitive and functional decline. It is a diagnosis of exclusion, thus reversible causes of dementia such as B12 deficiency, CNS infections and thyroid disorders need to be ruled out. Neuroimaging should be done to detect neoplasms and vascular disease. Other forms of dementia such as Lewy body disease, frontotemporal degeneration and Parkinson disease are also included in the differential. Epidemiological studies have clearly shown that age is the predominant risk factor for AD. The incidence rises exponentially above 65 with nearly half the population above 85 with the diagnosis [2]. AD is usually preceded by a condition called mild cognitive impairment (MCI), which is characterized by mild memory loss with preservation of other cognitive and functional activities. MCI is an important component in the continuum from healthy cognition to dementia. Predictors that mild cognitive impairment will lead to AD include carrying the e4 allele, brain atrophy and the presence beta-amyloid deposits [22]. Recently proposed diagnostic revisions incorporate imaging and the presence of CSF biomarkers to confirm AD but these are not yet routinely recommended [23]. A recent observational study supports the use of CSF biomarkers for diagnosing

AD highlighting their good positive predictive value [24]. The use of biomarkers can potentially yield specific and sensitive information for the diagnosis of early AD as well as help follow its clinical course. Plasma biomarkers such as macroglobulin and complement factor have increased expression in AD patients but their sensitivity, specificity and lack of reproducibility have limited their use in practice. Other plasma derived signal transduction proteins are currently under investigation [25]. The multifactorial nature of AD has added to the difficulty of discovering practical biomarkers. CSF derived biomarkers such as oligomers of beta-amyloid and tau have shown more promise for early detection of AD [26]. In addition CSF biomarkers of oxidative stress such as products of lipid peroxidation have shown some promise in observational studies [27].

Biomarkers and imaging will likely play a larger role in the management of AD in the future. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and monitoring of AD [16]. Over 200 papers have been published by this initiative. Biomarkers from both the CSF and plasma have been investigated [28]. These include complement proteins, fibrinogen and phospholipids [29,30]. Biomarkers hold promise for detecting pre-clinical disease, monitoring disease course and response to therapy and facilitating the development of new therapies.

## AD and Oxidative Stress

Oxidative stress occurs when there is an imbalance between the production and quenching of free radicals from oxygen species. These reactive oxygen species (ROS) play a role in many chronic diseases including mitochondrial diseases [31], neurodegenerative diseases [32,33], renal disease [34], arteriosclerosis [35,36], diabetes [37], cancer [38] and SLE [39,40]. The process of aging is also associated with increased oxidative stress [41]. Through pathological redox reactions ROS can denature biomolecules such as proteins, lipids and nucleic acids. This can initiate tissue damage via apoptosis and necrosis. Oxidative stress plays a central role in the pathogenesis of AD leading to neuronal dysfunction and cell death [33]. Peripheral markers of oxidative stress are elevated in AD indicating that the damage is not brain-limited [42,43]. One study suggested that the level of oxidative markers is directly related to the severity of cognitive impairment [44]. The increased level of oxidative stress in the AD brain is reflected by increased protein and DNA oxidation, enhanced lipid peroxidation, decreased level of cytochrome c oxidase and advanced glycosylation end products. Lipid peroxidation can weaken cell membranes causes ion imbalance and impair metabolism. Oxidative stress can influence DNA methylation which regulates gene expression [45]. Internalized beta-amyloid may play a role in this process [14]. The trigger for oxidative stress is an active area of current research. The natural process of aging likely contributes by making the brain more vulnerable to oxidative insults but other factors are necessary [46].

Recent evidence suggests that disruption of metal homeostasis may also contribute to oxidative stress [47,48]. During aging the brain accumulates metals such iron, zinc and copper which act as antioxidants. Metal dependent enzymatic processes are important for brain metabolism and there is evidence that this process is disrupted in AD brains [47]. The natural role of beta-amyloid is not clearly defined. One study showed that in cell-free systems beta-amyloid can act as an antioxidant inhibiting the formation of hydroxyl radicals preventing lipid and protein oxidation in rat mitochondria [49]. Metal chelation

appeared to be an important part of the mechanism. Beta-amyloid binds with redox active metals such as copper, zinc and iron triggering signaling cascades that mediate cellular physiology. By promoting conformational changes, copper binding can facilitate beta-amyloid aggregation which is influenced by its redox state [47]. Synaptic zinc has been associated increasing plaque burden in AD mouse models [50]. There is evidence that disruption of zinc homeostasis may play an important role in microtubule and tau pathology [51]. Zinc and iron can bind tau and promote aggregation and phosphorylation [52]. These findings support the investigation of beta-amyloid-specific metal-complexing agents and antioxidants as possible disease-modifying agents [53]. Metal chelators such as clioquinol and desferrioxamine have had some success in altering the progression of AD [54,55].

Mitochondrial dysfunction, which is associated with an accumulation of ROS, appears to play a role in the early events of AD pathology [56,57]. There is evidence from AD mouse models and postmortem brains that suggest the loss of mitochondrial integrity plays an important role in synaptic dysfunction [58]. Both structural and metabolic changes, including increased fragmentation and decreased fusion, have been observed in the AD brain [57]. Mitochondria are essential for the formation and maintenance of synapses. There is evidence that oxidative damage precedes pathological changes [59]. Oxidation of mitochondrial DNA renders it more susceptible to somatic mutation as oxidized bases are frequently misread during replication [60]. These mutations may initiate erroneous beta-amyloid processing [61]. If the natural function of beta-amyloid is to act as an antioxidant, it may be that the early oxidative stress triggers this compensatory mechanism which over time leads to the pathological lesions. A recent study, using mouse models, showed that mitochondria-targeted antioxidant catalase helps prevent abnormal beta-amyloid processing decreasing plaque burden [62]. There is also evidence that beta-amyloid deposits lead to more mitochondrial damage [63]. Beta-amyloid peptide has been shown to inhibit cytochrome oxidase leading to disruption of the electron transport chain and production of ROS [64]. Thus a vicious cycle may be initiated that culminates in progressive disease. The importance of mitochondrial dysfunction in AD pathology has been getting considerable attention. Links between mitochondrial function, tau phosphorylation, and beta amyloid amyloidosis are increasingly being recognized. Focusing on the mitochondria will identify alternative therapeutic targets that could lead to early therapeutic interventions [65].

Despite the overwhelming evidence that links oxidative stress and AD, antioxidant therapies have limited success in clinical trials [66-69]. Antioxidants have shown neuroprotective effects in vitro and mouse models but these are not matched with clinical data. Supplements such as vitamin E, coenzyme Q10 and melatonin have been studied as well as dietary antioxidants, such as phenolic compounds. A prospective study of 4740 participants showed that the vitamin E and C supplements in combination was associated with reduced AD prevalence and incidence. No evidence of a protective effect was observed with use of vitamin E or vitamin C alone [70]. The protective association of vitamin E seems to be related to the absence of the APOE epsilon 4 allele [71]. Other factors contributing to the lack of efficiency may include blood-brain barrier permeability, inappropriate timing of administration or suboptimal drug levels at the target site in the central nervous system [67]. Due to the irreversible progression of AD, treatment initiated late in the course of disease is unlikely to be beneficial.

## Future Prospects

Current studies are focusing on rational modifications of antioxidants

and combining them with other supplements or drugs for synergistic effects. Antioxidant agents that directly target the mitochondria are also being developed [72]. Mitoquinone mesylate is one such compound that has been shown to prevent cognitive decline, decrease oxidative stress and reduce beta-amyloid accumulation in mouse models [73]. The anti-aging protein Sirtuin1, which is involved in regulating cellular senescence, is another potential target. Its activity is decreased during oxidative stress [74]. Polyphenols are neuroprotective compounds that enhance its activity and are currently being investigated [75]. Concerns such as bioavailability, biotransformation, synergy with other dietary supplements, and possible pro-oxidant activities still need to be addressed. There is evidence that yeast selenium supplements protect the brain from oxidative damage in animal models [76]. Clinical trials are being planned. Other antioxidants that are currently being investigated by clinical trials include Epigallocatechin-Gallate, Pramipexole and Lipoic Acid plus Omega-3 Fatty Acids. Clinical trials are also investigating whether the use of antioxidant therapy can be monitored with CSF biomarkers [77]. In one clinical trial antioxidant treatment did not appear to influence tau or beta-amyloid burden but did lower oxidative stress in the brain [78]. The clinical effect and possible risk factors of this is still under investigation. Identifying oxidative stress early in those patients at risk of developing AD is critical for disease modifying therapy. Biomarkers and imaging are being investigated as potential tools to identify high risk patients [79,80].

## Summary

AD is the most common cause of dementia and the incidence is currently on the rise. Sporadic AD, which is the most common form, results from the combination of genetic factors and epigenetic events. AD is a progressive, debilitating course of which there is no current effective disease modifying therapy. Acetylcholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists are the current standard of therapy. These may mildly improve quality of life but have generally been disappointing [81]. Despite inflammation being at the heart of AD pathogenesis, a recent meta-analysis concluded that neither aspirin, NSAIDs nor steroids significantly affects cognitive decline in AD patients [82]. Although many questions remain unanswered regarding the pathogenesis of this disease and its relationship to aging, oxidative stress clearly plays an important role.

There is increasing evidence from genetic, immunohistochemical and proteomic that the complement system has an important role in the pathogenesis of AD. This system is closely related to inflammation and the production of reactive oxygen species underscoring the importance of oxidative stress in AD pathology. Recent therapeutic investigations include metal ionophores designed to reduce oxidative stress caused by disruption of metal homeostasis as well as agents that specifically target the mitochondria. Interactions between metals and cytotoxic beta-amyloid beta are known to occur but a further elucidation of the associated cellular changes is still needed. The role metals play in the oxidative stress of AD and the development of therapeutic interventions targeted to restore metal balance are active areas of current investigation. Studies in animal models of the disease with antioxidants report significant improvements of their AD-like phenotype. Although epidemiologic studies show that dietary intake of antioxidants reduces the risk of AD, clinical trials with antioxidants show only a marginal positive or no effect [83]. These therapies target underlying processes that are active before the clinical signs of dementia, thus must be given in the early stages [33,84]. The recent focus on mitochondrial dysfunction at the heart of AD pathology may lead to new therapeutic targets for early intervention [56,57]. Most patients diagnosed with

AD already have significant irreversible damage, thus early screening and intervention are likely to be critical in the management of these patients.

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